REACTION OF NITROPARAFFINS WITH PSEUDO BASES AND IMINES

BY

GERHARD WALTER LEUBNER

B.S., Union College, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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IN THE GRADUATE COLLEGE OF THE
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ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Dr. Nelson J. Leonard for his advice and encouragement during the course of this investigation.

The author also desires to thank the University of Illinois for a teaching assistantship in 1945-1946 and the Eli Lilly Company for fellowships from 1946 to 1948.

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Introduction

In the alkaloid field some 1-nitromethyl-1,2,3,4-tetrahydroisoquinolines have been synthesized by the reaction of pseudo bases, or isoquinolinium salts and potassium hydroxide, with nitromethane (1). The object of this investigation was to attempt to prepare similar compounds using nitromethane and the other common nitroparaffins. These compounds could then be converted to compounds containing a 1-aminomethyl group by reduction of the nitro group, and this could be followed by alkylation. Similar compounds in the quinoline series should be possible through the same series of reactions. Several structural arrangements are present in such molecules which make their testing for pharmacological activity of interest. The ethylenediamine structure which is present in both series suggests possible antihistamine activity. The combination of the tetrahydroisoquinoline structure, and the fact that both of the nitrogen atoms present are beta to the benzene nucleus are suggestive of possible anesthetic activity.

Since 1-anilino-2-nitro-1-phenylethane, which had been prepared by the addition of nitromethane to benzalaniline (2), had structural similarities to the isoquinoline condensation products, this series of compounds was also investigated.

Discussion Of Results

The reaction of 2-methylisoquinolinium iodide with the nitroparaffins and potassium hydroxide was investigated. With 2 mole equivalents of potassium hydroxide an amorphous solid was obtained from which 2-nitronaphthalene was isolated in 7.8-9% yield by sublimation or by chromatagraphy. A mechanism for its formation has been proposed. Two other products were isolated, one by distillation and the other by chromatography or by recrystallization, but they have not

been identified. The latter was obtained in a very good yield when only 1.1 mole equivalent of potassium hydroxide was employed, but it was impure (m.p. 104-111°) and all attempts to purify it were unsuccessful. Kaufmann (3) had reported a compound, obtained using 2 mole equivalents of alkali, with a melting point of 99° and implied that it was 2-methyl-1-nitromethyl-1,2-dihydroisoquinoline. It is very doubtful that he had a pure compound. Nitroethane and 1-nitropropane gave the di-condensation products 1,1-*bis*-(2-methyl-1,2-dihydroisoquinolyl) nitroethane and 1,1-*bis*-(2-methyl-1,2-dihydroisoquinolyl)-1-nitropropane in yields of 41-44% and 20% respectively. These results were unexpected in that di-condensation occurred even with a five-mole excess of nitroparaffin present. All reported cases of this reaction have given mono-condensation products. 2-Nitropropane appeared not to react.

The preceeding compounds were dihydroisoquinolines. Some of the corresponding reactions were studied in the tetrahydroisoquinoline series with 2-methyl-3,4-dihydroisoquinolinium iodide or the corresponding pseudo base 1-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. The former was prepared by oxidation of 2-methyl-1,2,3,4-tetrahydroisoquinoline with iodine and potassium acetate in alcohol solution. A new method was found for the preparation of 2-methyl-1,2,3,4-tetrahydroisoquinoline which is much more convenient than the method reported in the literature and gives comparable yields. It involves catalytic reduction of isoquinoline and methylation of the resulting 1,2,3,4-tetrahydroisoquinoline with formaldehyde and formic acid. The pseudo base was prepared by treatment of an aqueous solution of 2-methyl-3,4-dihydroisoquinolinium iodide with sodium hydroxide.

The reaction of 2-methyl-3,4-dihydroisoquinolinium iodide, potassium hydroxide and nitromethane or nitroethane gave oils which could not be purified. Similar results were obtained using the corresponding isolated pseudo base. The reaction of the pseudo base with phenylnitromethane gave an 87.2% yield of crystalline 2-methyl-1-(α-nitrobenzyl)-1,2,3,4-tetra-

hydroisoquinoline.

During picrate formation of the condensation product from 1-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline and nitromethane, cleavage occurred to form 2-methyl-3,4-dihydroisoquinolinium picrate. This result led to an investigation of the picrates of other nitromethane-pseudo base condensation products. Proof has been obtained that the picrates reported by Hope and Robinson (1) as anhydrocotarninenitromethane picrate and anhydrohydrastininenitromethane picrate are actually cotarine and hydrastinine picrate, the nitromethane condensation products having been cleaved during picrate formation. Anhydrocotarninenitromethane picrate was obtained in ether solution but cleavage occurs upon attempted recrystallization.

When so much difficulty was encountered in attempts to obtain the desired compounds by pseudo base condensations, 1-dimethylaminomethyl-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline was synthesized from Reissert's isoquinoline compound, 2-benzoyl-1-cyano-1,2-dihydroisoquinoline, by the procedure of Rupe and Frey (4) with some modifications. The overall yield from isoquinoline was only 1.9%.

At the same time the analogous reactions were carried out in the quinoline series. Most of this work was reported originally by Rupe and coworkers (5), but our results differed from theirs in several instances. During the reduction of Reissert's compound or the isoquinoline compound a benzoyl group migrates from one amino group to another. A mechanism has been proposed for this reaction. Hydrolysis of the reduction product, 2-benzoylaminomethyl-1,2,3,4-tetrahydroquinoline, gave 2-aminomethyl-1,2,3,4-tetrahydroquinoline. Upon methylation of the latter with methyl iodide and potassium hydroxide Rupe, *et al.* (5) had obtained 2-aminomethyl-1-methyl-1,2,3,4-tetrahydroquinoline, 2-dimethylaminomethyl-1-methyl-1,2,3,4-tetrahydroquinoline and the methiodide of the latter. In this reaction our results gave a dimethylated amine which appeared to be 1-methyl-2-methyl-

aminomethyl-1,2,3,4-tetrahydroquinoline from the results obtained upon methylation of 2-aminomethyl-1-methyl-1,2,3,4-tetrahydroquinoline, a second liquid which was probably the mono-methylated amine 2-aminomethyl-1-methyl-1,2,3,4-tetrahydroquinoline, and the quaternary salt 2-dimethylaminomethyl-1-methyl-1,2,3,4-tetrahydroquinoline hydriodide. The melting point found for the monopicrate of 2-dimethylaminomethyl-1-methyl-1,2,3,4-tetrahydroquinoline also disagreed with that reported by Rupe. An attempt to further methylate the dimethyl product was unsuccessful. The possibility of other methods of methylation was considered, but attempts to methylate the model compound 1,2,3,4-tetrahydroquinoline with formaldehyde and reducing agents were unsuccessful.

The addition of nitroparaffins to benzalaniline has been investigated. Nitromethane gave 65-80% yields of the addition compound. The new compounds 1-anilino-2-nitro-1-phenylpropane and 1-anilino-2-nitro-1-phenylbutane have been prepared in yields of 30% and 55% from nitroethane and 1-nitropropane, respectively. 2-Nitropropane has given an unidentified solid. No products were obtained in the reaction of the imines benzalazine, benzophenone anil and hydrobenzamide with nitromethane.

Chemical and catalytic reductions of 1-anilino-2-nitro-1-phenylethane and anilinophenylacetonitrile were investigated in an attempt to prepare 2-anilino-2-phenylethylamine. The latter was prepared in 20-25% yield by either catalytic reduction with platinum oxide in acetic anhydride or by lithium aluminum hydride reduction of the aminonitrile. It was also prepared in smaller amounts by similar reductions of the nitroamine. The hydrogenolysis products aniline and N-benzylaniline were also obtained in some of the reductions of both compounds. Attempted methylations of 2-anilino-2-phenylethylamine were unsuccessful.

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VITA

The author was born on August 31, 1921 in Walton, New York, where he received his elementary and high school education. He entered Union College of Schenectady, New York in September, 1939, and received the Bachelor of Science Degree in Chemistry in April, 1943. During the summer of 1942 he was employed as a control chemist in the Kodachrome film processing plant of Eastman Kodak Company at Chicago. After spending two and one-half years as a chemist in the organic research department of Winthrop Chemical Company, Rensselaer, New York, he entered the University of Illinois in October, 1945. During the fall and spring semesters of 1945-1946 he was a half-time teaching assistant in the analytical department. From October, 1946, until July, 1948, he held the Eli Lilly Research Fellowship.